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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/556,127	04/20/00	KURANE	R 0163-0750-0X

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EXAMINER	
FREEMAN, J	
ART UNIT	**PAPER NUMBER**
1655	13

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/556,127	Applicant(s) Kurane et al
	Examiner Jeffrey Fredman	Art Unit 1655

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Aug 16, 2001* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-72* is/are pending in the application.

4a) Of the above, claim(s) *1, 12-14, 16-20, 22, and 27-45* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *2-11, 15, 21, 23-26, and 46-72* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *12*
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

Claim Objections

1. Claims 25, 26 are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim cannot depend from a multiple dependent claim. See MPEP § 608.01(n). Accordingly, the claims have not been further treated on the merits.

Claim Rejections - 35 USC § 112

2. Claims 50-52, 56-58 and 64-65 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 50 recites the limitation "oligoribonucleotide of said probe" in line 2. There is insufficient antecedent basis for this limitation in the claim.

It is vague and indefinite what is meant by "chemiric" in claims 51 and 64.

It is vague and indefinite what is meant by "robe" in claim 56, line 2.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 2-7, 9, 46-48, 50 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Morrison et al (Anal. Biochem. (1989) 183:231-244).

Morrison teaches a nucleic acid probe which is labelled with either fluorescein or pyrenebutyrate at either the 5' or 3' end (see Table 1), and where the probe has a base sequence such that a C is in the 3' terminal position, and also 1 nucleotide from the 3' or 5' position, such that there will be a G residue in the target at the corresponding position upon hybridization (page 236, table 1). Further, the 5' labeled probes are inherently extendible in a polymerase extension reaction because the 3' end is unblocked. With regard to 3' ends, the probes of Morrison are identical in structure to those claimed and disclosed in the specification and therefore inherently meet the extendible limitation as well as the claimed probes. Morrison teaches probes which have a G at the 5' end and probes which have a C at the 3' end for labelling (page 236, table 1). The probes of Morrison are chemically modified by the addition of a fluorescent label (page 236, table 1).

5. Claims 2-9, 15, 46-50, 53, 59-63, 66 and 72 are rejected under 35 U.S.C. 102(e) as being anticipated by Wittwer et al (U.S. Patent 6,140,054).

Wittwer teaches a nucleic acid probe which is labelled with either fluorescein at the 3' end or with CY5 at the 5' end (column 21, lines 1-5). The Wittwer probe of SEQ ID NO: 5 has fluorescein attached to the 3' terminal nucleotide, which is a C and has a C 1 nucleotide from the end nucleotide (column 21, lines 1-5). Wittwer states that some of the labelled probes can function as primers (column 3, lines 41-47). Wittwer also teaches a probe, SEQ ID NO: 6, which

has a CY5 at the 5' end and a G is present at the 5' end and 3 nucleotides distant from the 5' nucleotide. Further, the SEQ ID NO: 6 probe is phosphorylated at the 3' end. unblocked The probes of Wittwer are chemically modified by the addition of a fluorescent label (column 21, lines 1-5). Wittwer teaches placement of the probes into kits (column 35, claim 7).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 2-11, 15, 46-53, 59-66 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer in view of Metelev et al (Bioorganic and Medicinal Chemistry Letters (1994) 4(24):2929-2934).

Wittwer teaches the limitations of claims 2-9, 15, 46-50, 53, 59-63, 66 and 72 as discussed above. Wittwer does not teach the use of 2'-O-methyloligoribonucleotides in a chimeric oligonucleotide probe.

Metelev teaches the use of 2'-O-methyloligoribonucleotides in a chimeric oligonucleotide probe (page 2930, figure 1).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probe of Wittwer with the 2'-O-methyloligoribonucleotides of Metelev since Metelev states "In summary, incorporation of 2'-O-methyloligoribonucleotides into PS-oligonucleotides increases nuclease stability and affinity to the target RNA (page 2933).". An ordinary practitioner would have been motivated to make the Wittwer probes chimeric with 2'-O-methyloligoribonucleotides in order to achieve the express advantages of increased nuclease stability and, where needed, increased affinity to RNA.

8. Claims 2-9, 15, 21, 46-50, 53, 54, 59-63, 66, 67 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer in view of Hogan et al (U.S. Patent 5,030,557).

Wittwer teaches the limitations of claims 2-9, 15, 46-50, 53, 59-63, 66 and 72 as discussed above. Wittwer does not teach the use of helper probes.

Hogan teaches methods for enhancing hybridization including the use of helper probes within ribosomal RNAs (column 4, lines 44-68). Hogan also teaches requirements for helper probes (columns 5 and 6).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Wittwer probes with the helper probe and probe methods of Hogan into a kit since Hogan teaches that "Thus, by using a properly selected helper oligonucleotide, the rate of hybridization between the probe and its complementary sequence in the targeted nucleic acid can be substantially increased and even permit hybridization to occur at a rate and under conditions otherwise adequate for an assay where, without the use of the helper, no substantial hybridization can occur.(column 4, lines 36-43). Hogan explicitly states that the helper probe need not be targeted at a unique sequence (column 7, lines 40-42). An ordinary practitioner would have been motivated to add the helper probe to the Wittwer kit in order to increase the rate of hybridization.

9. Claims 2-9, 15, 23, 24, 26, 46-50, 53, 55, 56, 58-63, 66, 68, 69, 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer in view of Tyagi et al (U.S. Patent 6,150,097) and further in view of Donovan et al (U.S. Patent 5,874,587).

Wittwer teaches the limitations of claims 2-9, 15, 46-50, 53, 59-63, 66 and 72 as discussed above. Wittwer does not teach placement of the probes on a solid support nor the dual labeled quenching probe.

Tyagi teaches molecular beacon type probes, with with nucleic acid probes which comprise two fluorescent dyes of different kinds and which are quenched when not hybridized but emit fluorescence upon hybridization (columns 3-8).

Donovan teaches placement of fluorescent probes onto arrays (column 12, lines 44-67). Donovan expressly teaches placement of molecular beacons of Tyagi as taught by Tyagi above, onto two dimensional arrays, using multiple different probes with multiple different labels which emit light of different wavelengths (column 12, lines 44-67).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the Wittwer probes or the Tyagi probes into an array as taught by Donovan since Donovan states that such an array "can be used in a single assay to carry out an extensive survey of an amplified genomic region (column 12 lines 64-65)". An ordinary practitioner would be motivated to form an array to survey a particular desired sequence as expressly suggested by Donovan.

10. Claims 2-9, 15, 23-26, 46-50, 53, 55-63, 66, and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer in view of Tyagi et al (U.S. Patent 6,150,097) and further in view of Donovan et al (U.S. Patent 5,874,587) and further in view of Heller et al (U.S. Patent 6,017,696).

Wittwer in view of Tyagi and further in view of Donovan teach the limitations of claims 2-9, 15, 23, 24, 26, 46-50, 53, 55, 56, 58-63, 66, 68, 69, 71 and 72 as discussed above. Wittwer in view of Tyagi and further in view of Donovan do not teach the use of a heater to contol probe movement.

Heller teaches the use of temperature for stringency control (column 7, lines 1-5) and Heller teaches the use of electrodes, which when in operation will increase temperature, to control

stringency (column 7). Heller further teaches the use of sensors such as thermocouples (column 48).

It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine the probe device of Wittwer in view of Tyagi and further in view of Donovan with the hybridization control methods of Heller since Heller states "The active nature of the devices provides independent electronic control over all aspects of the hybridization reaction (column 5, lines 64-66)". An ordinary practitioner would have been motivated to control temperature in order to control stringency of hybridization.

Response to Amendment

11. The Declaration under 37 CFR 1.132 filed August 16, 2001 is insufficient to overcome the rejection of the claims based upon 35 USC 102 or 103 as set forth in the last Office action because:

The declaration, while technically not drawn to the new rejections necessitated by the IDS and by the amendments is not persuasive for several reasons. First and foremost, the declaration is apparently intended to demonstrate an unexpected result using the Bodipy FL label relative to fluorescein. However, since the claims are not limited to the use of the Bodipy FL label, and in fact expressly include fluorescein in the Markush groups, the claims are not commensurate in scope with any asserted unexpected result. Second, the data presented in the declaration directly conflicts with the data presented in the table in the specification. That is, the data in the declaration shows that Bodipy FL is reduced in fluorescence by 83% while fluorescein is only

reduced by 40%. However, Table 4 on page 77 shows a different result, that fluorescein is reduced 90% and Bodipy FL 95%. This data supports the position that there is no functional difference between fluorescein and Bodipy FL. Therefore, the declaration is not persuasive with regard to any claim.

Response to Arguments

12. Applicant's arguments with respect to the claims have been considered but are moot in view of the new ground(s) of rejection.

The only argument remaining is whether the objection to the claims has been avoided by amendment. Claims 25 and 26 still are multiply dependent from claim 23, which is itself multiply dependent from claims 2 or 5. Therefore, this objection remains proper and these claims are not treated.

Conclusion

13. Applicant's submission of an information disclosure statement under 37 CFR 1.97(c) with the fee set forth in 37 CFR 1.17(p) on August 16, 2001 which included the Morrison reference prompted some of the new ground(s) of rejection presented in this Office action. Applicant's amendment necessitated the remaining new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 609(B)(2)(i). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeff Fredman, Ph.D. whose telephone number is (703) 308-6568.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, W. Gary Jones, can be reached on (703) 308-1152.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Application/Control Number: 09/556,127

Art Unit: 1655

Papers related to this application may be submitted to Group 180 by facsimile transmission via the P.T.O. Fax Center located in Crystal Mall 1. The CM1 Fax Center numbers for Group 1800 are either (703) 305-3014 or (703) 308-4242. Please note that the faxing of such papers must conform with the Notice to Comply published in the Official Gazette, 1096 OG 30 (November 15, 1989).

Jeffrey Fredman
Primary Patent Examiner
Art Unit 1655

August 24, 2001